REMARKS

Claims 5 to 13 are cancelled. Claim 1 has been amended to recite at least one complement activating anti-tumor antibody "directed to the tumor cells or antigens of said tumor cells." Support for this amendment can be found throughout the Specification, in particular, on page 13, lines 17 to 19 and page 30, lines 15 to 21. Claim 1 has further been amended to clarify administering to a patient in need of suppressing or eliminating tumor cells. Support for this amendment is found throughout the Specification, in particular, at page 7, line 30 to page 8, line 2. Support for newly added claims 16 and 17 can be found throughout the Specification, in particular, at page 30, lines15 to page 31, line 5 and page 33, lines 6-15. Support for newly added claim 18 is found throughout the Specification, in particular, at page 57, lines 21 to 23. The newly added Claims 16, 17 and 18 read on the elected species.

Rejection of Claims 1-4 and 13-15 Under 35 U.S.C. § 112, First Paragraph

Claims 1-4 and 13-14 are rejected under 35 U.S.C. § 112, first paragraph, because the Specification while being enabling for the treatment of mammary carcinoma (Specification page 8, Figure 5A-5D), the Specification does not reasonably provide enablement for the treatment of other tumor types. The Specification does not enable any person skilled in the art to which it pertains, or with which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The Examiner cited the *Wands* factors (*In re Wands*, 8 USPQ 2d 1400, 1404 (CAFC 1988)). Applicant disagrees with the reasoning for the rejections and has addressed the *Wands* factors under the appropriate headings, as applied to the amended claims.

The Nature of the Invention and the Breadth of the Claims

The basis of the Examiner's rejection is that one skilled in the art would not believe that a single agent could treat all tumor types. The rejection relies on the teaching of the Cecil reference stating that for various known cancer types there is not one specific chemotherapeutic agent or combination that is effect at treating or inhibiting the growth of every type of cancer. However, the amended claims recite the use of the combination of neutral soluble glucan with a complement activating antitumor antibody directed to the tumor cells or antigens of said tumor

cells and this combination is not a single agent as that term is used in the Cecil reference. Each complement activating antitumor antibody has specificity to certain tumor cells or certain antigens on tumor cells, and it is these specific cells that would benefit from Applicant's combination of soluble glucan with complement activating antitumor antibody. Applicant submits that the amended claims address the Examiner's concern. It is not a single agent that could treat all tumor types but rather a combination of neutral soluble glucan and a complement activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells for suppressing or eliminating tumor cells. As shown in the Examples of the Specification, specific antibodies are directed to specific cancers. The results shown in FIGs. 5A to 5D are exemplary of the methods of the invention.

Applicant discovered that neutral soluble glucans work with each antitumor antibody that has specificity for a particular tumor targeted. Although, the term "antitumor antibody" reflects a general category of antibodies, a specific antibody is intended for each type of tumor and that antibody is selective or specific to that tumor. Thus, neutral soluble glucan can be combined with a variety of antitumor antibodies that each are directed to or specific for a certain type of tumor. Thus, the tumor cell to be treated specifies the type of complement activating antitumor antibody one can use in the claimed invention.

In determining an appropriate antibody, the Specification sets forth certain characteristics, such as complement activation, that the antibody must possess for it to be useful in the present invention. The inventor has determined the basic mechanism of action for the combination of neutral soluble glucan and antitumor antibodies as set forth in the claims. Thus, the Specification provides a general description of the type of antibody that works in the present invention, which in turn provides a reasonable expectation of success. The number of candidate antibodies is described in the Specification (See page 19, line 24 to page 23, line 19) and thus do not include all antibodies but a narrowed class defined by the characteristics described. Thus, the antitumor antibodies as recited in the claims are a described class of antibodies that can be tested for the properties needed to practice the invention with simple and routine *in vitro* tests. Given the specific guidance in the Specification, such test for determining the necessary properties would be considered routine in the antibody art if such property where not already known. Therefore, there is no need for extensive, undue experimentation.

The Amount of Direction or Guidance and Presence or Absence of Working Examples

Applicant's disclosure provides ample guidance and direction to practice the invention. As stated above, the Specification provides guidance to carry out Applicant's invention and sets forth working examples. In support of Applicant's position, Applicant directs the Examiner attention to a post-filing published journal article, Li *et al.,* "Combined Yeast ß-glucan and Antitumor Monoclonal Antibody Therapy Requires C5a-mediated Neutrophil chemotaxis Via Regulation of Decay-Accelerating Factor CD55," *Cancer Res:* 67: (15) 7421-7430 (2007) (Exhibit A, provided herein). This reference discloses the administration a yeast glucan with antitumor monoclonal antibodies using human carcinomas (non-small-cell lung carcinoma and human ovarian carcinoma) implanted in immunocompromised severe combined immunodeficient mice. The reference demonstrates combined therapy (glucan and antitumor monoclonal antibody) with human non-small-cell lung carcinomas and when further combined with anti-CD 55 showed tumor regression and increased survival in a SKOV-3 human ovarian carcinoma model. The teachings of the Li *et al.* reference demonstrate that one of skill in the art with the guidance provided in Applicant's Specification can readily apply Applicant's invention of glucan and antitimor antibody therapy to other cancer models. In summary, the guidance provided in the Specification is sufficient for one skilled in the art to practice Applicant's claimed invention without undue experimentation as indeed practiced by the cited reference.

The State of the Prior Art and the Predictability or Unpredictability of the Art

The Examiner considers the art to be unpredictable. However, even if this is true, the patent statutes do not require absolute predictability, only that it would not require undue experimentation to practice the claimed method. The post filing reference (*i.e.,* Li *et al.,* discussed above) provides the necessary evidence that undue experimentation is not required to practice the claimed method.

The Level of Skill in the Art and the Quantity of Experimentation Necessary

While the level of skill in the art is deemed high, the antibody art has been recognized as a field that routinely tests for identification and properties of an antibody. (See *In re Wands*).

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The standard for determining whether the specification meets the enablement requirement is whether the experimentation needed to practice the invention is undue or unreasonable. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicant's disclosure meets these requirements. The Specification has ample guidance with working examples. Evidence of such guidance for practicing Applicant's claimed invention is provided by the Li *et al.* publication.

Further, the *Wands* factors are analyzed when undue experimentation has been raised. However, these factors are intended to be illustrative factors not mandatory. The factors that may be relevant in the analysis are dependent upon the facts. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1213. The facts presented herein, show that the desired characteristics of the anti-tumor antibodies and the underlying basic mechanism of action as taught in the Specification provide sufficient guidance for a skilled artisan to develop or ascertain the type of antibodies for use with the present invention. In light of the above discussion, the combination of neutral soluble glucan and an antitumor antibody could not be considered a "single agent for all tumor types" and given the guidance in the Specification would not require undue experimentation for treatment of various tumor types. The scope of the amended claims is enabled.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-4 and 13-14 Under 35 U.S.C. § 103 (a)

Claims 1-4 and 13-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jamas *et al.* (U.S. Patent No. 5,532,223) in view of Leyland-Jones (The Lancet, Oncology Vol. 3, March 2002).

According to the present rejection, one of ordinary skill in the art would have been motivated to combine the teachings of the references because both are directed to the treatment

of tumors and the idea of combining the teachings flows logically from having been individually taught by the prior art. Applicant respectfully disagrees with this premise.

In *KSR v. Teleflex*, 127 S.Ct. 1717, 82 USPQ2d 1385 (2007), the court clarified the appropriate analysis for determining obviousness under 35 U.S.C. § 103. The court restated that the Graham framework controls the analysis. Explicit findings as to (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, etc., should be made in the Graham analysis. The legal question of obviousness is then assessed against this factual background.

The claimed invention would not have been obvious over the cited references because none of the references, either individually or in combination teaches, suggests or would have motivated the skilled artisan to arrive at a method of suppressing or eliminating tumor cells, comprising administering to a subject in need of treatment to suppress or eliminated tumor cells, a neutral soluble glucan and at least one complement activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells, wherein the glucan does not induce inflammatory cytokines and the glucan and antibody suppresses or eliminates tumor cells. The claims will now be analyzed under the Graham indicia with regard to the Jamas and Leyland-Jones teachings.

Scope and Content of the Prior Art

Jamas *et al.*

The Jamas reference relates to neutral soluble ß-glucans which exert potent and specific hematopoietic and immunological effects without stimulating cytokines. In particular, the reference discloses methods for stimulating platelet proliferation. The Jamas reference generally discloses the use of neutral soluble preparations for administration to humans and animals as an anti-infective to combat infection associated with burns, surgery, chemotherapy, bone marrow disorders and other conditions in which the immune system may be compromised. The only teaching of the Jamas glucan in relation to treating cancer is directed to a patient type who is immunosuppressed and may get an infection that can be treated by the Jamas glucan. (See column 9, lines 24 to 33). The Jamas reference neither discloses or suggests the use of neutral

soluble glucan with a complement activating anti-tumor antibody for suppressing or eliminating tumor cells or for tumor regression.

Leyland-Jones

The Leyland-Jones article describes generally the use of trastuzumab in the treatment of solid tumors, as a single-agent, as a second line or as a third line treatment. When trastuzumab is used as a first-line agent it is used in combination with cytotoxic chemotherapy drugs (*e.g.*, taxanes, platinum analogs etc.) and hormone therapy. See page 141, last two paragraphs to page 142 first paragraph. There is no suggestion or expectation of success of using the combination of glucan with trastuzumab, as is claimed by Applicant.

Differences Between Prior Art and Claims at Issue

The rejection is based on "an obvious to try rational" because the rejection assumes that each reference teaches one component of Applicant's combination for use with tumors and therefore one would logically know to try the two components. This assumption is in error. The Jamas reference does not teach direct suppression or elimination of tumor cells with the glucan disclosed by Jamas. Jamas *et al.* teaches the administration of glucan for its anti-infective properties.

While the Leyland-Jones reference does suggest combination therapy for trastuzumab, the only classes of compounds suggested for combination are cytotoxic agents and hormones. The courts have applied the "obvious to try" rational on situations where there is a "finite" number of solutions to the problem and such solutions are identified and predicable. See *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341 (Fed. Cir. 2007). The teachings of Leyland-Jones describe a finite combination of solutions that includes cytotoxic agents and hormones for use with trastuzumab. Leyland-Jones is silent to other possible combinations. Thus, neither reference identifies Applicant's suggested combination. Therefore, no motivation is found in either reference to substantiate the rejection's assumption.

Level of Ordinary Skill in the Art

The level of ordinary skill in the art is high.

Secondary Considerations

Additionally, neither reference suggests that neutral soluble glucan acts with antitumor antibodies to suppress or eliminate tumors or cause tumor regression, as is recited in Applicant's claims. Applicant directs the Examiner's attention to the Exemplification, in particular, the results shown in FIGs. 11A and FIG 15-22. These results were demonstrated with combined treatment on various tumor models and antibodies. For example, FIG. 11A shows the results of glucan with the antibody 3F8 IgG3 anti-Gd2 ganglioside on RMA-S lymphoma, FIG. 15 shows that beta glucan enhances regression of EL-4 hepatic lymphoma when combined with 3F8 IgG3 anti-Gd2 ganglioside monoclonal antibody. FIGs. 18A –C demonstrate glucan therapy with 11CI anti MMTV monoclonal antibody on Pta64 tumor cells (A); RMA-S-Muc1 Therapy with 14G2a anti GD2 monoclonal antibody (B) and RMA-SMuc 1 therapy with BCP8 IgG anti-Muc 1A antibody (C). FIG. 21 shows enhanced tumor regression mediated by glucan with antitumor antibody (BCP8 IgG 2b anti Muc 1) on Lewis Lung Carcinoma cells. The results show an enhanced effect on the tumor in the presence of glucan and antibody combination over each component alone.

In view of the foregoing, a *prima facie* case of obviousness has not been established because there is no teaching, suggestion or motivation of a method of suppressing or eliminating tumor cells, comprising administering to a subject in need of treatment to suppress or eliminate tumor cells a neutral soluble glucan and at least one complement activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells, wherein the glucan does not induce inflammatory cytokines and the glucan and antibody together suppress or eliminate tumor cells. Thus, the references whether considered alone or in combination do not render Applicant's invention obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In summary, the cited art does not render Applicant's invention obvious. In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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